

Remarks

Claims 1-3, 5-8, 11, and 12 are pending in the application. Claim 6 is amended above to correct a typographical error in lines 1 and 3 replacing "liver" with "live". Further, claims 6 and 7 are amended above to replace the phrase "mannitol or sorbitol or a mixture of them" with the phrase "mannitol or sorbitol or both of them" to maintain consistency in the claim language with that of pending claim 3. This amendment does not affect the scope of the claims, as the phrases are interchangeable. However, in an abundance of caution, Applicants wish to maintain consistency in use of the phrases so that no one is in a position to later argue that, by virtue of the different phrasing, the claims must have been intended to have a difference scope. New claims 13-19 are presented in dependent form, presenting new combinations of limitations which had already been found in previously pending claims. Upon entry of this amendment, claims 1-3, 5-8, and 11-19 will be before the Examiner.

Applicants respectfully request reconsideration of the objections to claims 3, 6, and 7 set forth at page 2 of the Office Action. The claims as amended recite "or both of them" when referring to mannitol and sorbitol. Contrary to what is asserted in the Office Action, this phrase is not extraneous, as it refers only to mannitol and sorbitol. The phrase "of any of the foregoing" is associated with the phrase "alkali metal salts" which itself is affiliated with a list of amino acids. By definition, "any of the foregoing" refers to what precedes that phrase, and not what follows the phrase. Accordingly, reconsideration is respectfully requested.

Applicants next respectfully traverse the §102 rejection of claim 1 over Funkhouser *et al.* set forth at page 2 of the Office Action. In support of their traversal, Applicants note that neither Funkhouser '912 nor Funkhouser '110B1 disclose a lyophilized hepatitis A live vaccine formulation. Since claim 1 requires that the hepatitis A live vaccine be lyophilized, and since lyophilization is not taught or suggested by either of the Funkhouser patents, the Funkhouser patents cannot anticipate claim 1. Applicants respectfully request reconsideration and withdrawal of this rejection.

Claims 1-3, 6, 7, 11, and 12 stand rejected at pages 3-4 of the Office Action as obvious over Chiba-ken *et al.* Applicants respectfully traverse. Chiba-ken *et al.* teach a highly purified, stabilized, inactivated HAV (strain KRM 003). Chiba-ken do not suggest using a live HAV in the formulation, and certainly provide no reasonable expectation of success. As is well known to those skilled in the art, inactivated hepatitis A virus has completely different structural and functional properties as compared to a live attenuated HAV. An inactivated HAV of Chiba-ken *et al.* is only a protein envelope from which immunogenicity is generated, having no proliferative or infectious abilities. Stabilizing an

inactivated virus thus involves merely retaining key aspects of the tertiary structure of a protein envelope, and therefore is much more straightforward than stabilizing a live virus. Those skilled in the art recognize that a vaccine based on a live virus is entirely different from an inactivated virus. Not only is there a protein envelope to be maintained, there is also a nucleic acid core that must retain its replicative properties for the live virus to remain proliferative and infectious. As recognized by those skilled in the art, there are several advantages to live vaccines as compared to inactivated vaccines. For example, with a live vaccine, one can use a lower dosage and smaller number of doses. (See, for example, Funkhouser '912, column one, lines 50-60). It is well known that HAV is a small picornavirus without any lipoprotein outer envelope. Like the majority of live enteroviruses, HAV presented in the form of an aqueous suspension will rapidly lose its ability of replication or propagation, and thus will lose its infectious potency. Therefore, it is desirable to prepare not only a live HAV vaccine, but also a lyophilized HAV vaccine. The subject inventors are the first to provide a stabilized, lyophilized live attenuated HAV vaccine. Before the teachings of the subject application, no one knew how to protect a live picornavirus through the lyophilizing process. Accordingly, in the absence of Applicants' teachings, there has been no expectation of success provided by the prior art. Contrary to what is implied in the Office Action, Applicants do not rely on mere hypothesis for disputing the sufficiency of Chiba-ken *et al.* It is undeniable that the art has long desired a live HAV vaccine. (See, for example, the Funkhouser patents.) Chiba-ken *et al.* was published 10 years before the priority date of the subject application. Given the undeniable desire for a live HAV vaccine, and the time period between the publication of Chiba-ken *et al.* and the priority date of the subject application, there are two possibilities: (1) those skilled in the art did not have an expectation that a live attenuated HAV could be substituted for the inactivated HAV protein envelope of Chiba-ken *et al.*; or (2) someone attempted to substitute a live HAV for the inactivated HAV of Chiba-ken *et al.* and failed. The Examiner is invited to identify any other possibilities. In either case, Chiba-ken *et al.* is legally insufficient to support an obviousness rejection of the claimed invention. To support an obviousness rejection one must find both the suggestion and the expectation of success, in the prior art. *In re Dow Chemical Co.*, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988). The mere fact that some of the same classes of ingredients are present in the Chiba-ken *et al.* formulation and in those claimed herein is not sufficient. There is simply no teaching in the prior art that would provide the requisite expectation of success to render the claimed invention obvious. Accordingly, reconsideration and withdrawal of this rejection is respectfully requested.

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Finally, Applicants gratefully acknowledge the Examiner's indication that claims 5 and 8 would be allowable if rewritten in independent form.

In view of the foregoing, Applicants believe that all claims currently pending are in condition for allowance, and such action is respectfully requested.

The Commissioner is hereby authorized to charge any fees under 37 CFR 1.16 or 1.17 as required by this paper to Deposit Account 19-0065.

Applicants invite the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephone interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,



Jeff Lloyd  
Patent Attorney

Registration No. 35,589

Phone No.: 352-375-8100

Fax No.: 352-372-5800

Address : 2421 N.W. 41<sup>st</sup> Street, Suite A-1  
Gainesville, Florida 32606-6669

JL/srp